REMARKS

Rejection of Claims 1-9, 11-31, 33, 39-40 and 53 Under 35 U.S.C. § 112, Second Paragraph:

The Examiner has rejected Claims 1-9, 11-31, 33, 39-40 and 53 under 35 U.S.C. § 112, second paragraph, contending that the recitation of "A method to protect a mammal from a disease...consisting of administering a formulation...to a mammal having said disease" is vague, because it is allegedly unclear how a mammal can be protected from a disease it already has.

Applicants initially note that the phrase "to protect a mammal from a disease" is defined in the specification on page 22, line 6, to page 23, line 12, wherein the phrase is defined to include more than simply *prevention* of disease. Nonetheless, the claims have been amended to remove the phrase found objectionable by the Examiner, which should render this rejection moot.

Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-9, 11-31, 33, 39-40 and 53 under 35 U.S.C. § 112, second paragraph.

Objection to the Specification and Rejection of Claims 1-9, 11-31, 33, 39-40 and 53 under 35 U.S.C. § 112, first paragraph:

The Examiner has objected to the specification and rejected Claims 1-9, 11-31, 33, 39-40 and 53 under 35 U.S.C. § 112, first paragraph, contending that the specification is insufficient to enable one of skill in the art to practice the claimed invention without undue experimentation. Specifically, the Examiner initially contends that the specification presumably treats Th2 mediated diseases by administering a heat shock protein that skews the immune response toward Th1. The Examiner submits that the specification teaches that *M. leprae* HSP-65 can induce a T cell response and that administration of this HSP can abolish airway hyperresponsiveness. The Examiner goes on to comment on page 4 of the Office Action about the "Th1/Th2 paradigm", noting many some investigators consider it to be overly simplistic. The Examiner appears in this paragraph to be challenging whether the claimed use of the heat shock protein to protect a mammal from a Th2-mediated disease has merit or has been enabled or whether it might be dangerous. The Examiner further contends that even assuming the truth of the Th1/Th2 paradigm, that many of the diseases specifically recited in the claims cannot be considered to be strictly Th2-mediated, specifically referencing atopic dermatitis (argument supported by Shimada et al.), interstitial lung disease

hypersensitivity pneumonitis (argument supported by Nance et al.), and intrinsic asthma (argument supported by Mandic et al.). Finally, the Examiner contends that Rha et al. teach that of five HSPs tested, only *M. leprae* HSP had any immunological activity, and that Francis et al. teach that some HSPs can induce a Th2 response.

Applicants traverse the rejection of Claims 1-9, 11-31, 33, 39-40 and 53 under 35 U.S.C. § 112, first paragraph. Initially, Applicants note that, solely to expedite prosecution, and without any intent to prejudice or disclaim any future claims to the use of other HSPs, the claims have been limited to the administration of *M. leprae* HSP-65. With regard to Francis et al., Applicants submit that this publication shows that administration of an HSP peptide elicits a Th1 response when administered intranasally, and both a Th1 and a Th2 response when administered intraperitoneally in IFA. It appears from the comments of Francis et al. that the use of IFA is impacting the type of response, which would limit the Examiner's conclusions that HSPs are inducing a Th2 response *per se*. For example, Francis et al. state on page 342, col. 2, paragraph 2 of Discussion: "It has been known for more than 30 years that immunization with antigens in IFA favours the production of what are now known as Th2-dominated responses."

With regard to the other issues raised by the Examiner in this rejection, Applicants first wish to clarify that, in addition to demonstrating that the administration of *M. leprae* HSP-65 abolishes airway hyperresponsiveness in a mammal and induced a T cell response as the Examiner notes, the specification also demonstrates that the administration of *M. leprae* HSP-65 abolishes eosinophilic airway inflammation (*e.g.*, see Example 5), upregulated interferon-γ (IFN-γ) and IgG2a (*e.g.*, see Example 4), and downregulated production of interleukin-4 (IL-4) and IL-5 (*e.g.*, see Example 4). Applicants have attempted to clarify the invention by amending the claims to more particularly recite these effects of the claimed method.

With regard to the Examiner's comments regarding the Th1/Th2 paradigm, Applicants have not argued for a simplistic view of Th1-type and Th2-type immune responses, and do not intend to present a position that such responses are simplistic. Instead, Applicants have provided a novel method for regulating specific physiological activities, each of which is correlated with the etiology of, or is a direct symptom of, certain inflammatory conditions. Applicants' position is that administration of a heat shock protein according to the claimed method has the ability to reduce

eosinophilia, to reduce airway hyperresponsiveness associated with an inflammatory response, and/or to reduce a "Th2-type" *response* in an individual (*e.g.*, which is more specifically described in the present specification in terms of up- or downregulation of particular cytokines and antibody isotypes, rather than focus on a particular T cell). The ability of the claimed method to regulate these various specific events can provide a therapeutic benefit to a patient who has a condition that is caused or mediated by eosinophilia, that is characterized by inflammation associated with these particular types of immune responses, and/or that results in airway hyperresponsiveness. Given the clear demonstration of the claimed effect on eosinophilia, airway hyperresponsiveness, and immune responses that are commonly considered to be "Th2-type" responses, Applicants submit that the specification is enabling for the claimed methods. Furthermore, while Claim 40 is directed to a reduction in a Th2-type response, which appears to be the main focus of the Examiner's argument, it is noted that Claim 1 and its dependents are directed to the reduction of *eosinophilia* in a mammal and Claim 39 is directed to the reduction of *airway hyperresponsiveness* in a mammal.

The Examiner makes a reference to Louzoun et al., which is a mathematical model that attempts to illustrate the complexities, particularly with regard to autoimmune disease, of Th1 and Th2 responses. The model of Louzon et al. characterizes a Th2 "steady state" (the "healthy state" if one considers autoimmune disease) and a Th1 "steady state" (the autoimmune state), whereby the "steady state" type is influenced by T cells, cytokines and other immune system cells (*i.e.*, the whole system of influences rather than a single cell type), and where the model observes shifts from one steady state to another and back as various events manipulate the system. This model does not seem to cast any doubt on the ability of a given event (*e.g.*, administration of an agent) to cause a particular effect and even to shift the "steady state" of the system from a Th2-type to a Th1-type or vice versa. Moreover, this model does not negate experimental evidence provided by the present specification that shows that administration of a heat shock protein to a mammal that has eosinophilia, inflammatory immune reactivity that is commonly considered to be "Th2-type", and airway hyperresponsiveness, causes a significant reduction in the eosinophilia and airway hyperresponsiveness, and causes a significant shift from the indicators of the Th2-type response to those that indicate a Th1-type response. Indeed, one could even consider the Th2-type steady state of Louzoun et al. to be the "unhealthy" steady state relative to allergy, and observe a shift from this

steady state to a Th1-type steady state (healthier with regard to allergy) by the administration of heat shock protein.

Burnet et al. contend that an attempt to skew the Th1/Th2 ratio might be dangerous on a more global basis that allergen-specific Th1 responses might increase the incidence of autoimmune disease. However, such a concern does not negate the utility or even the value to the patient suffering from a hypereosinophilic or inflammatory condition, for example, of using HSP to reduce eosinophilia, airway hyperresponsiveness, and/or to try to shift the "steady state" of an inflammatory response in a mammal to, for example, lessen the effects of certain cytokines on the inflammatory status of a tissue. The method is intended to reduce eosinophilia, a hallmark of certain inflammatory conditions, such as allergy, and/or to reduce the inflammation and/or airway hyperresponsiveness that can be associated with such conditions. Indeed, the enclosed response to Burnet et al. by Wohlleben and Erb state that even though there might be serious side-effects, this issue has not been resolved clearly, and that the possibility of allergen-specific Th1 responses should not be discarded totally as a potential approach to anti-allergy vaccination.

Therefore, rather than arguing about the relative contributions of Th1-type versus Th2-type responses to various diseases, and even though the immune system is complex and may be viewed by some in the art as a complex shifting of "steady states" characterized by shifts in cells, cytokines and events, it is Applicants' position that the presently claimed invention is enabled even if one considers such complexities. The present specification enables one of skill in the art to practice the claimed method, directed to reduction of eosinophila, airway hyperresponsiveness, and/or a Th2-type response in a mammal by administration of *M. leprae* HSP-65. Any debate over the complexity of the Th1/Th2 paradigm, or speculation about whether the T cells involved in such responses are markers, rather than effectors, or whether the impact of regulating Th2-type versus Th1-type immune responses may have a negative impact on a different condition, does not negate the fact that reduction of eosinophilia, airway hyperresponsiveness and/or reduction of certain inflammatory responses is a useful therapeutic approach in a variety of conditions.

Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-9, 11-31, 33, 39-40 and 53 under 35 U.S.C. § 112, first paragraph.

Objection to the Specification and Rejection of Claims 1-9, 11-31, 33, 39-40 and 53 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has rejected Claims 1-9, 11-31, 33, 39-40 and 53 Under 35 U.S.C. § 112, first paragraph, on the basis of written description. The Examiner contends that the specification does not support the recitation of "at least one" pharmaceutically acceptable excipient. To expedite prosecution, Applicants have amended the claims to remove the phrase found objectionable by the Examiner.

Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-9, 11-31, 33, 39-40 and 53 under 35 U.S.C. § 112, first paragraph.

Applicants have attempted to respond to all of the concerns set forth in the October 27 Office Action and submit that the claims are in a condition for allowance. In the event that the Examiner has any further concerns regarding Applicants' position, he is encouraged to contact the below-named agent to expedite prosecution.

Respectfully submitted,

SHERIDAN ROSS P.C.

By: Angela Sebor

Angela Dallas Sebor
Registration No. 42,460
1560 Broadway, Suite 1200
Denver, CO 80202-5141
(303) 863-9700

Date: 27 April 2005